REMARKS

Claims 13-17 are all the claims pending in the application.

This amendment supplements and replaces the Amendment Under 37 C.F.R. § 1.116 filed January 6, 2004.

I. Request for Interview

Applicants respectfully request a personal interview with the Examiner prior to the issuance of the first Office Action. The purpose of the interview is to discuss the Examiner's position concerning obviousness of the present invention over Isner et al. and Morishita et al. in view of Ghodsi et al.

The Examiner is requested to contact the undersigned Applicant's representative to arrange a date for an interview.

II. Amendments to the Claims

In drafting the Amendment filed July 10, 2003, Applicants inadvertently miss-abbreviated Hemaglutinating Virus of Japan (HVJ) as "HJV" in claims 13-17. Please see the present specification, pages 26-29, and Morishita et al. (U.S. Patent No. 6,248,722), column 5 line 23, for the correct abbreviation.

Accordingly, claims 13-17 have been amended to change "HJV" to "HVJ." Entry of this amendment is respectfully requested.

III. Claim Rejections Under 35 U.S.C. § 103(a)

Claims 13-17 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Isner et al. (U.S. Patent No. 6,121,246 or WO 97/14307) (hereinafter "Isner") and Morishita et al. (U.S. Patent No. 6,248,722) (hereinafter "Morishita"), in view of Ghodsi et al. (Human Gene Therapy 9:2331 (1998)) (hereinafter "Ghodsi").

The present inventors have unexpectedly found that injection of VEGF and HGF genes into the subarachnoid space results in significant levels of protein expression in the brain, and have demonstrated successful therapeutic angiogenesis using VEGF and HGF gene therapy for treatment of cerebral occlusive disease.

Claims 13-17 of the present application recite therapeutic or preventative methods for cerebrovascular disorders comprising introducing hepatocyte growth factor (HGF) and/or vascular endothelial growth factor (VEGF) genes in the form of HVJ-liposomes by direct injection into the subarachnoid space.

In the Advisory Action dated January 26, 2004, the Examiner contended that the feasibility of delivering a genetic vector encoding a gene of interest to brain cells via the subarachnoid space has been taught by Ghodsi. The Examiner also stated that because of the presence of the blood-brain barrier, the subarachnoid route would have a higher expectation of success than intramuscular administration. Thus, the Examiner concluded that the claimed invention as a whole was prima facie obvious.

Similarly, the Examiner contended on page 4 of the October 6, 2003 Office Action that Isner teaches local injection of HGF and VEGF genes for treatment of cerebrovascular ischemia.

The Examiner also stated that Morishita teaches expression of HGF via HVJ-liposomes, use of HGF to treat many different diseases including nervous disorders and arterial diseases, and *in vivo* administration directly into brain tissue. Finally, the Examiner relied on Ghodsi for demonstrating introduction of a genetic vector directly into the subarachnoid space. Accordingly, the Examiner concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by Isner and Morishita by administering the HGF and/or VEGF genes in the form of HVJ-liposomes into the subarachnoid space with a reasonable expectation of success.

Applicants respectfully traverse this rejection, and assert that based on the references cited above, one skilled in the art would not have predicted with a reasonable expectation of success that HGF and/or VEGF genes administered in the form of HVJ-liposomes into the subarachnoid space would be effective for treatment of cerebrovascular disorders. Because of the unpredictability of gene therapy, a person skilled in the art at the time of the invention would not have expected HGF and/or VEGF genes injected into the subarachnoid space to be effectively expressed in the brain. In addition, because of the unique characteristics of the central nervous system, a person of ordinary skill in the art would not have reasonably expected that expression of HGF and/or VEGF genes would provide successful treatment for cerebrovascular diseases.

Isner and Morishita teach local injection of VEGF and HGF genes for treating ischemia. However, neither reference teaches injection into the subarachnoid space. At column 4, lines 2-7, Isner provides a list of diseases potentially treatable by the disclosed methods, and includes

cerebrovascular ischemia. However, the specification describes only intramuscular gene transfer. See Example 1. Similarly, Morishita states that HGF genes may be administered directly to diseased organs including the brain (see column 6, lines 5-11) but fails to demonstrate *in vivo* administration to any site other than cardiac muscle (see Test Example 8) and skeletal muscle (Test example 9). Thus, neither Isner nor Morishita enables gene transfer to the central nervous system. Further, although Ghodsi teaches the treatment of mucopolysaccharidosis by intracerebral injection of the β-glucuronidase gene, Ghodsi does not teach the treatment of cerebrovascular diseases, the use of VEGF or HGF genes, or gene therapy via HVJ-liposomes.

A skilled artisan would not have been motivated to combine the teachings of these references with a reasonable expectation of success in achieving the claimed invention, for at least the following reasons.

First, because gene therapy remains a highly unpredictable art, expression of VEGF and HGF in the brain was not predictable. The poor efficiency of gene transfection using viral vectors in the central nervous system, in particular, has limited the development of gene therapy in the brain. For example, Saitoh et al. note that "[g]ene therapies with VEGF and HGF to stimulate angiogenesis have been successful in muscle; however, efficacy in the CNS is unknown. *Gene transfection efficiency of viral vectors has been poor in the CNS,* and the safety of such vectors is questionable." Youichi Saitoh, et al., *Gene Therapy for Ischemic Brain Diseases,* Current Gene Therapy (2003), vol. 3, no. 1, pp. 49-58. abstract (emphasis added).

Although Ghodsi discloses successful intracerebral injection of the β-glucuronidase gene, this reference does not teach or suggest intracerebral injection of VEGF or HGF genes. In

addition, the adenoviral vector used in Ghodsi is clearly different from the non-adenoviral HVJ-liposomes used in the present invention. Thus, because both the gene being delivered (VEGF or HGF v. β-glucuronidase) and the mode of delivery (HVJ-liposomes v. adenoviral vector) are different, one of ordinary skill in the art would not have reasonably expected, based on Ghodsi, that injection of VEGF and HGF genes into the subarachnoid space would result in significant levels of VEGF and HGF protein expression in the brain.

Furthermore, successful treatment of brain diseases by HGF and/or VEGF gene transfection was unpredictable, because the structure and the diseases of the central nervous system differ significantly from those of other organs. For example, the brain is more susceptible to ischemia than the heart and other organs. See, e.g. Id., page 49. The above authors also point out that "to date, gene therapies reported to stimulate angiogenesis have been specific only to skeletal and cardiac muscles." Id. In addition, brain diseases are notoriously difficult to treat. Although cerebral hypoperfusion caused by cerebral occlusive disorders is known to lead to cerebral ischemic events, a clinically effective treatment has not yet been established. See Shen-ichi Yoshimura, et al., *Gene Transfer of Hepatocyte Growth Factor to Subarachnoid Space in Cerebral Hypoperfusion Model*, Hypertension, May 2002, vol. 39, pp. 1028-1034.

Thus, because of the fundamental differences between diseases of the brain and diseases of other organs, such as the skeletal and cardiac muscles disclosed in Isner and Morishita, success in inducing angiogenesis in ischemic heart and skeletal muscle, by intramuscular

transfection of HGF and/or VEGF genes, would not have led a skilled artisan to reasonably expect that gene therapy would prove to be an effective treatment for cerebral occlusive diseases.

In conclusion, the present inventors have unexpectedly found that HGF and/or VEGF genes transferred into the subarachnoid space can improve cerebral hypoperfusion, and that the transfection of HGF genes into the subarachnoid space can prevent delayed neuronal death. Given the unpredictability and poor efficiency of gene transfection in the central nervous system, a person of ordinary skill in the art would not have reasonably expected that injection of VEGF and HGF genes into the subarachnoid space would result in significant levels of protein expression in the brain. Furthermore, because of the fundamental differences between diseases of the brain and diseases of other organs, the heart and skeletal muscle effects described by Isner and Morishita would not have led a person of ordinary skill in the art to reasonably expect that VEGF and/or HGF gene therapy would be an effective treatment for cerebral occlusive diseases.

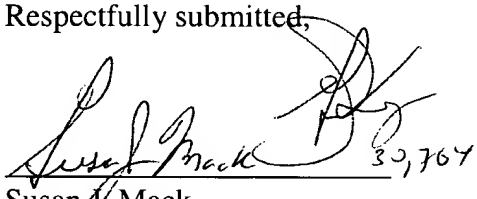
At best, the teachings of the references cited by the Examiner merely make it obvious to try gene therapy using HGF and/or VEGF administered into the subarachnoid space in the form of HVJ-liposomes for the treatment of cerebral occlusive diseases. However, the teachings do not provide a reasonable expectation of success. Thus, it would not have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by Isner and Morishita by administering the HGF and/or VEGF genes in the form of HVJ-liposomes into the subarachnoid space with a reasonable expectation of success.

In view of the foregoing, the claimed invention is not obvious over Isner and Morishita in view of Ghodsi. Accordingly, Applicants respectfully request withdrawal of the rejection.

Reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



Susan J. Mack
Registration No. 30,951

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: April 6, 2004